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PROSTACYCLIN INCREASES PORTAL VENOUS FLOW

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ABSTRACT

Prostacyclin (PGI_2) is a potent vasodilator and is a
potential therapeutic agent to increase blood flow during several
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significant decline in CO, FAP, and PAP occurred. Atropinization
further depressed CO. The most marked effect of PGI_2, however,
was an increase in PoVF without a change in PoVP. This effect
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anesthetized swine, PGI_2 is a potent vasodilator in all vascular
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ABSTRACT

Prostacyclin (PGI_2) is a potent vasodilator and is a potential therapeutic agent to increase blood flow during several disease states. PGI_2 is also elevated in plasma during sepsis or pancreatitis. The hemodynamic effect of PGI_2 has not been investigated with regard to the portal venous system. In five anesthetized swine, cardiac output (CO), central venous pressure (CVP), femoral artery pressure (FAP), heart rate (HR), pulmonary artery pressure (PAP), portal venous flow (PoVF), and portal venous pressure (PoVP) were measured before and after increasing doses of PGI_2. The infusions were then repeated after atropine administration The previously reported effects on the peripheral and pulmonary vascular systems were confirmed. After an injection of 0.5 to 5.0 ug/kg of PGI_2 into the left atrium, a significant decline in CO, FAP, and PAP occurred. Atropinization further depressed CO. The mos marked effect of PGI_2, however, was an increase in PoVF without a change in PoVP. This effect was more pronounced when atropine was administered. In anesthetized swine, PGI_2 is a potent vasodilator in all vascular beds, including the portal venous system. These hemodynamic changes should be realized when exogenous PGI_2 is considered as a therapeutic agent or when endogenous PGI_2 might increase in association with disease states like pancreatitis or sepsis.

INTRODUCTION

Prostacyclin (PGI_2), an unstable intermediate of arachidonic acid, is an inhibitor of platelet aggregation, and a potent hypotensive agent. The mechanism for PGI_2 vasoactivity is thought to be a decrease in resistance by vasodilation in man (1), monkey (2), dog (3), cat (4), rat (5), and pig (6). Because of its hemodynamic and anticoagulation effects, PGI_2 has been implicated as a potential therapeutic agent in a variety of conditions. PGI_2 also has been associated with pathologic conditions. We reported elevations of the PGI_2 metabolite $PGF_{1-alpha}$ in plasma and peritoneal ascites fluid during experimental hemorrhagic pancreatitis in the pig (7). When this ascites fluid was injected into the portal vein of a normal

anesthetized pig, the blood pressure and cardiac output significantly decreased and portal pressure increased (8). The portal venous effects of PGI_2 have not been reported.

The objective of the current study was to examine portal venous hemodynamic changes secondary to PGI_2. Also, we designed the study to observe and confirm systemic and pulmonary hemodynamic changes following increasing doses of commercially obtained synthetic PGI_2 in anesthetized pigs. We repeated the study after administering atropine because paradoxical bradycardia has been observed with hypotension following large PGI_2 doses in dogs (9). PGI_2 was confirmed to be a vasodilator in the systemic and pulmonary systems, but the major effect of PGI_2 was to dilate the portal venous system and increase portal venous flow.

MATERIAL AND METHODS

Abbreviations for the hemodynamic variables measured in this text (all are expressed as the mean values $\pm$SD):

CO	cardiac output	PAP	pulmonary artery pressure
CVP	central venous pressure	PoVF	portal venous flow
FAP	femoral artery pressure	PoVP	portal venous pressure
HR	heart rate		

Five domestic pigs of both sexes (15-25 kg) were anesthetized with intramuscular ketamine (0.45 mg/kg) and xylazine (0.45 mg/kg) as a preanesthetic analgesic, and endotracheal anesthesia of 50% O_2:50% N_2O with 0.5-1.5% methoxyflurane. Subsequently, a femoral vein polyethylene cannula (#8 French pediatric feeding tube, I.D.=1.8 mm, O.D.=2.8 mm, Seamless Hospital Products, Wallingford, CT) was advanced into the thoracic vena cava to measure CVP. With a similar catheter, the distal aorta was cannulated via the femoral artery to measure blood pressure (FAP) and obtain samples for blood gas determinations. A Swan-Ganz catheter was placed into the opposite femoral vein and threaded into the pulmonary artery for PAP measurements. With these pressure lines in place and the blood gas and acid-base status maintained within normal limits for swine (pH=7.5+0.5, pCO_2=40+5 torr, and PO_2>100 torr), the abdomen was opened and an electromagnetic flow probe (Carolina Medical Electronics, King, NC) was placed around the main portal vein. PoVF was measured continuously. A similar #8 French cannula was placed in the superior mesenteric vein to measure PoVP.

The arterial blood was again sampled to insure that the blood gas levels were within normal limits before a midline sternotomy was accomplished and the pericardial sac opened. The Swan-Ganz catheter was manipulated into the pulmonary artery until a pulmonary artery tracing was obtained. A left atrial #8 French polyethylene cannula was placed via the left atrial appendage for administration of PGI_2 (Upjohn Co., prostacyclin sodium salt U-53217A, Lot #14813-BDT-118A). An electromagnetic flow probe (Carolina) was then placed around the ascending aorta for continuous measurement of CO.

All pressures were continuously monitored via pressure transducers (model P23Db, Statham Instruments, Inc., Medical Division, Oxnard, CA) with a Gould Brush 2000 recorder (Gould, Inc., Instrument Systems Division, Cleveland, OH). All flow probes were monitored via a flow meter (Carolina) and recorded with the Gould Recorder.

PGI_2 was stored as the sodium salt at $-15^{\circ}C$ and then dissolved, immediately before injection, in 0.05 M Tris buffer at pH 8.6 and $4^{\circ}C$. No hemodynamic response was seen when 10 ml of buffer was given to each animal before injection of PGI_2 for the dose response curve. We constructed a dose response curve by using increasing doses of PGI_2 (0.005, 0.05, 0.5, and 5.0 ug/kg) given through the left atrial cannula. Baseline and response pressures and flow values were recorded every 10 seconds to 120 seconds after injection of PGI_2. When a hemodynamic response to PGI_2 occurred, the duration was less than five minutes. Fifteen minutes were allowed between each of the four injections of increasing PGI_2 doses. Then the animal received 0.1 mg/kg (10) of atropine intravenously and, after 5 minutes, another set of dose responses were obtained by using the same doses listed above.

The maximum percent change ($\%MAX\Delta$) of each hemodynamic variable was calculated for each PGI_2 dose before and after atropine. These figures were then tested by a two-way analysis of variance (ANOVA) to determine the relative significance of the effects of PGI_2 dose and atropinization and to make certain there was no interaction between the relative hemodynamic response before and after atropinization.

A one-way ANOVA for repeated measures was used to determine at what dose a significant change from baseline first occurred and then a Dunnett's test for multiple comparisons (11) was applied to indicate the time interval after injection when the hemodynamic variable significantly changed.

RESULTS

The two-way ANOVA F ratios and p values are listed in Table 1. Significant changes ($p<0.05$) occurred in the $\%MAX\Delta$ with increasing PGI_2 doses in the hemodynamic variables FAP, PAP, CO, and PoVF. If atropine had been previously administered, the $\%MAX\Delta$ in CO and PoVF were significantly different from the response without atropine in CO and PoVF. The latter was of borderline significance ($p=0.055$). An interaction between increasing PGI_2 dose and the absence or presence of atropine was not seen in any hemodynamic variable.

Table 2 lists the dose of PGI_2 which resulted in the first significant ($p<0.05$) change from baseline values, the F ratio indicating this significance, and the duration of the significant change during the 120-sec observation period. After injection into the left atrium, the lowest PGI_2 dose that caused significant hemodynamic change was 0.05 ug/kg. An increasing number of measurements beginning with FAP, PoVP, and PoVF became statistically significant with increasing PGI_2 doses. The reaction sequence for the 5.0 ug/kg bolus dose without atropine, where the largest number of significant hemodynamic changes occurred, is shown in Figure 1. For illustration purposes, rather than depict the entire time course for each hemodynamic variable for each PGI_2 dose before and after atropine, we present the maximum deviation from baseline ($\%MAX\Delta \pm SD$) for each hemodynamic variable (Figures 2-4). In this way, the direction of that change can be expressed for all doses before and after atropine.

On consideration of all hemodynamic responses, PGI_2 ultimately decreased pressure in every measured vascular bed: systemic, pulmonary central venous, and portal (Fig. 2a-d). Besides the reduction in systemic pressure, an increase in PoVF was the most pronounced effect of PGI_2 before atropine (Fig. 3b). This elevation was higher after atropine ($p=0.055$, Table 1). Even though a dose-related bradycardia was seen in isolated cases, a significant HR change was not found before or after atropine (Fig. 4).

Table 1. Two-way ANOVA %MAXΔ of hemodynamic variables*

Hemodynamic variable*	Dose F (p)	Atropine status F (p)	Interaction F (p)
FAP	23.68 (0.000)	0.04 (0.848)	0.61 (0.614)
PAP	7.80 (0.001)	0.48 (0.494)	0.39 (0.761)
CVP	2.31 (0.095)	0.40 (0.532)	0.59 (C 625)
PoVP	1.09 (0.366)	1.00 (0.326)	0.12 (0.947)
CO	4.81 (0.007)	7.09 (0.012)	1.13 (0.292)
PoVF	3.28 (0.033)	3.96 (0.055)	0.16 (0.921)
HR	1.41 (0.255)	0.08 (0.780)	2.42 (0.084)

*Abbreviations: FAP = femoral artery pressure; PAP = pulmonary artery pressure; CVP = central venous pressure; PoVP = portal venous pressure; CO = cardiac ouput; PoVF = portal venous flow; HR = heart rate.

Table 2. First dose (ug/kg) with significant change from baseline*

	Before atropine			After atropine		
	First dose	F-ratio	Time(sec)	First dose	F-ratio	Time(sec)
Pressures (torr)						
FAP	0.05	6.4	20 to 50	0.05	3.1	40 to 90
PAP	0.05	3.4	60 to 120	0.5	6.5	30 to 120
CVP	5.0	4.0	70 to 120	5.0	15.5	70 to 120
PoVP	0.05	3.8	20 to 30	none	...	...
Flows (ml/min)						
CO	0.5	3.6	80 to 120	0.5	5.9	40 to 120
PoVF	0.5	11.1	20 to 110	0.05	3.5	20 to 50
Rates (beats/min)						
HR	none	...	...	none	...	...

*Abbreviations: FAP = femoral artery pressure; PAP = pulmonary artery pressure; CVP = central venous pressure; PoVP = portal venous pressure; CO = cardiac output; PoVF = portal venous flow; HR = heart rate.
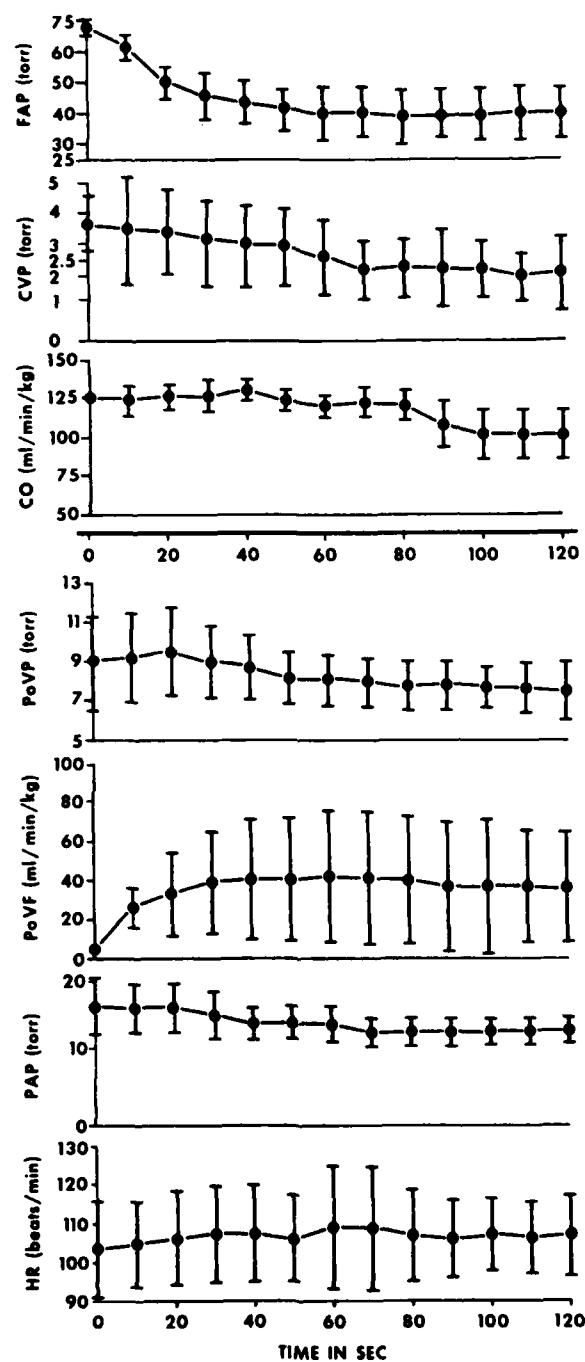
Figure 1. The reaction sequence over time in seconds for 5.0 μg/kg PGI$_2$ dose without atropine is depicted for all 7 measured hemodynamic variables (±SD). More hemodynamic variables showed significant changes from baseline values at the 5.0 μg/kg dose than at the 0.005, 0.05, or 0.5 μg/kg dosages.
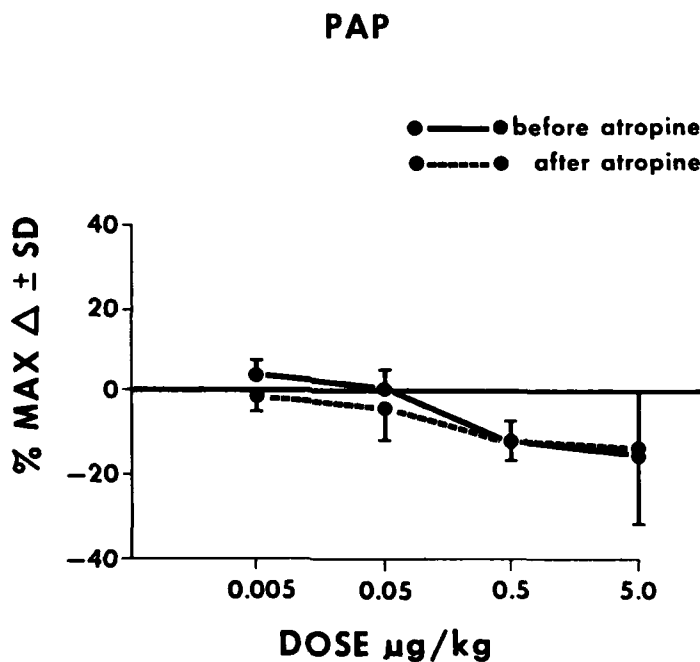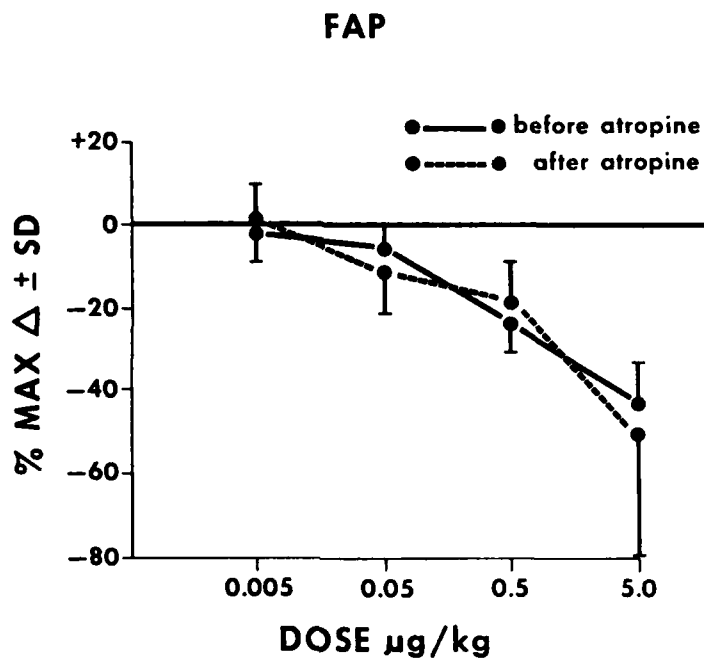
FAP

PAP

Figure 2A (top). The log dose response curve of femoral artery
pressure (FAP). Figure 2B (bottom). The log dose response curve of
pulmonary artery pressure (PAP). Both figures show the maximum
deviation from baseline values expressed as a percentage (%MAXΔ ±SD).

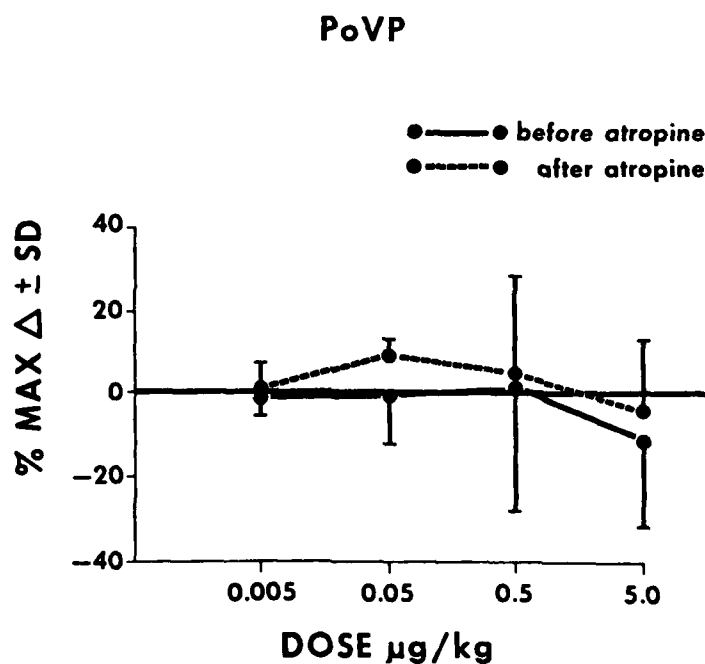--Figure 2 continued next page.

Figure 2 continued from preceding page. Figure 2C (top). The log dose response curve of central venous pressure (CVP). Figure 2D (bottom). The log dose response curve of portal venous pressure (PoVP). Both figures show the maximum deviation from baseline values expressed as a percentage (%MAXΔ ±SD).

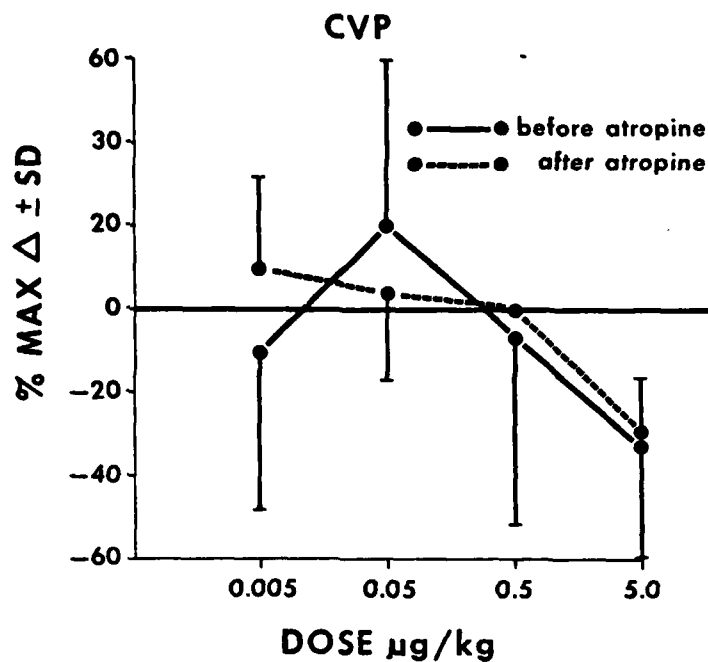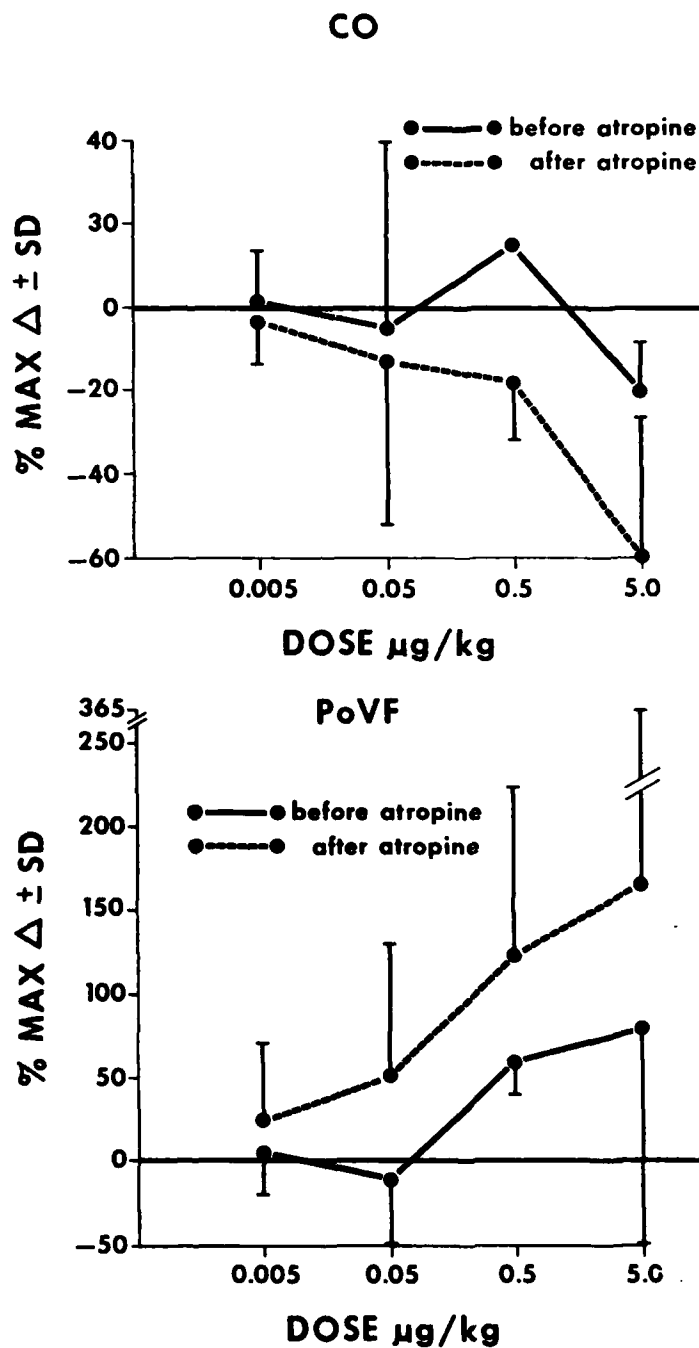Figure 3A (top). The log dose response curve of cardiac output (CO).
Figure 3B (bottom). The log dose response curve of portal venous flow
(PoVF). Both figures show the maximum deviation from baseline values
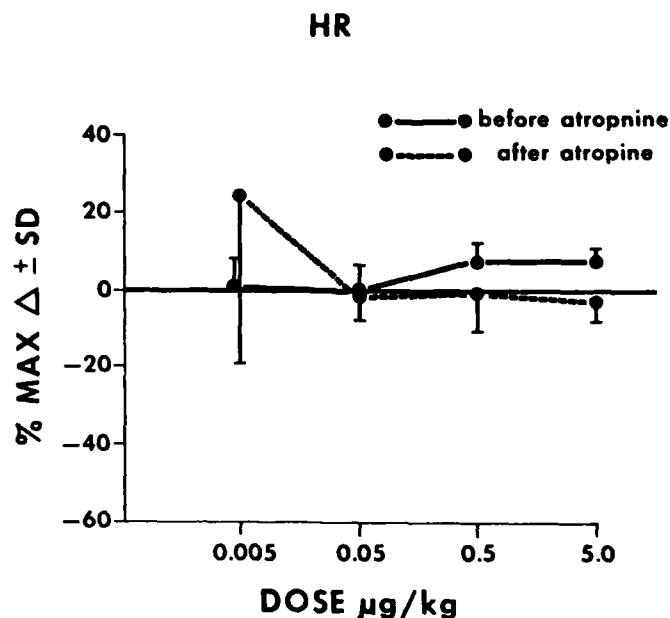(%MAXΔ ±SD) without and with atropine.

HR

Figure 4. The log dose resopnse curve of heart rate is shown by using the maximum deviation from baseline values (%MAXΔ %SD) without and with atropine.

DISCUSSION

Prostacyclin is a potent vasodilator in the anesthetized pig when administered into the left atrium. The first hemodynamic variable to change significantly from baseline was FAP, showing a threshold dose of 0.05 ug/kg. Initially, we attempted injections through the right atrium but did not observe a vascular response until 128 ug/kg was used. Other workers (12) have described this increased response to arterial over venous administration in the pig and attributed it to pulmonary degradation. This result is in contrast to that of Kubo et al (13); they found no differences in the hemodynamic response after infusion of PGI_2 (from 0.02 to 1.0 ug/kg) into the right or left atrium in both conscious and anesthetized sheep. Rats and rabbits also display this lack of pulmonary degradation (14). The contrasting results of this species variability cannot yet be explained. In all studies, however, including ours, the fall in FAP, CVP, and PAP plus the decline in CO were dose-dependent. The increase in PoVF was also dose dependent and has not been previously reported.

The overall PGI_2 hemodynamic response in this study can be explained by first observing the sequence of vascular changes after PGI_2 and before atropine administration (Fig. 1). After bolus

injection in the left atrium, the PGI_2 first reached the systemic vasculature. A marked decline in blood pressure was observed. The mesenteric arterial system was dilated, increasing blood flow into the portal venous system. This was reflected by a slight increase in PoVP and a marked increase in PoVF. Presumably, the outflow channels to portal venous blood (hepatic venules) were also dilated to allow for the increase in PoVF without a marked increase in PoVP. These vascular changes began to occur within the first 20 sec. At 30 sec, the CVP and PAP began to fall and this venous and pulmonary hypotension was associated ultimately with a fall in CO. A fall in CVP and PAP, despite the increased portal flow into the central venous system, can be explained by the dilatation in the central venous and pulmonary arterial systems. The sequence of hemodynamic responses shown in Figure 1 is interpreted by us to indicate that preload falls due to right-sided blood pooling. The result is a fall in CO.

Mean HR increased only slightly during the hypotension of this study before or after atropine (Fig. 4). The expected tachycardia following hypotension was probably blunted by the anesthesia as Kubo et al (13) reported in conscious as compared to anesthetized sheep receiving PGI_2. The lack of tachycardia may be considered a relative bradycardia during hypotension and anesthesia. A PGI_2-induced vagal reflex on HR has been postulated in the pentothal anesthetized pig but atropine was not used (12). HR response to PGI_2 in conscious humans has been described as a dose-related tachycardia, although an occasional reversal to sudden bradycardia has been noted (15). In dogs, PGI_2 causes an anomolous bradycardia (16) not dependent upon anesthesia (17) and partly mediared by vagal pathways (18). An elevation of HR has been reported in conscious dogs (19), ponies (20), and in anesthetized neonatal (21) and adult (12,22) pigs. The lack of HR changes before and after atropine in the current study probably represent a heart unable to respond to hypotension during anesthesia.

PGI_2 produced a marked increase in PoVF accompanied by relatively little change in PoVP. These results indicate the potential for mesenteric and heptic vasodilation with this prostanoid, consistent with other studies in which it lowered mesenteric vascular resistance in dogs (23). Although an increase in mesenteric flow after PGI_2 has been reported as dose-related in dogs (24,25), the canine liver showed no increase in hepatic artery flow ar reported in two radiomicrosphere studies (26,27). In humans, by way f contrast, total liver blood flow as determined by the indocyanine green method increased dramatically in response to low dose PGI_2 infusion (28). Our data for portal flow in pigs coincide with this observation. In hemorrhagic shock, PGI_2 reportedly increases hepatic flow to above preshock levels (29) and increased survival in at least one hypovolemic hypotension model (30). This beneficial effect may be secondary to the redistribution of blood flow during hypotension. During

hypotension, blood flow bypasses the mesenteric circulation because of portal and mesenteric vasoconstriction; this results in an increase in PoVP and presumably a decrease in PoVF (31).

Infusion of PGI_2 after atropinization resulted in a greater elevation in PoVF and a greater decline in CO than before atropine. The antimuscarinic effects of atropine on smooth muscle may have allowed even further hepatic and mesenteric vasodilatation. The portal system acted as a conduit to this increased flow into a further dilated venous system. The result was a further decline in CO.

If PGI_2 were administered for an unrelated disease when cirrhosis, portal hypertension, and esophageal varices were present, flow into the portal system would increase and possibly initiate variceal hemorrhage. The portal venous effects of PGI_2 should be realized when considering this prostanoid as an exogenous therapeutic agent. The dynamics of endogenous PGI_2 should also be considered in certain disease states. Pancreatitis (7) and sepsis (32) have both been associated with increased PGI_2 levels in the plasma. Even before PGI_2 was characterized as a separate biochemical entity, pancreatitis was known to result in an increase in prostaglandins (33) or an increase in phospholipase A_2 which could increase prostaglandin synthesis (34,35). The normovolemia of these disease states can be quickly converted into relative hypovolemia by inflammatory fluid loss into the interstitial space and the panvasodilatation of PGI_2. Thus, the PGI_2 hemodynamic changes in all vascular beds should be considered when PGI_2 is or will be present from an endogenous or exogenous source.

Prostacyclin (PGI_2) is a potent vasodilator in all vascular beds. Besides a fall in systemic and pulmonary pressures, a marked increase in portal venous flow occurs in the anesthetized swine model of this study. These hemodynamic changes should be realized when exogenous PGI_2 is considered as a therapeutic agent or when endogenous PGI_2 might increase in association with disease states like pancreatitis or sepsis.

CONCLUSION

PGI_2 is a potent vasodilator of the portal venous system in swine besides its well-inown vasodilatory activity in the systemic and pulmonary vascular beds.

RECOMMENDATION

The role of PGI_2 in the expected hemodynamic response following shock and trauma or inflammatory diseases should be investigated further.

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